

Interagency Assessment of Oxygenated Fuels



in high-dose Sprague-Dawley rats that were administered MTBE by gavage, supports the finding of an exposure-related increase in F344 rats that were exposed to MTBE by inhalation, even though the latter strain exhibits a high spontaneous rate of these benign tumors. The lack of a tumor response in the testes of rats that were given TBA in their drinking water suggests that exposure to the parent compound, rather than to this metabolite, may be the cause of this effect. The finding of kidney tumors in male F344 rats exposed to MTBE by inhalation is supported by a similar response in male F344 rats treated with TBA. The lack of a kidney tumor response in Sprague-Dawley rats treated with MTBE by olive oil gavage at doses that were lower than those used in the inhalation study may be due to differences in target organ dosimetry of the causal agent. Pharmacokinetic studies may help explain this difference in response.

The reported increase in lymphomas and leukemia in female rats given MTBE by gavage is supported by the increase in these tumors in Sprague-Dawley rats administered formaldehyde via their drinking water and suggests a possible involvement of this metabolite in the leukemogenic effect of MTBE. In addition to the reported positive response in Sprague-Dawley rats, there is also a negative drinking water study of formaldehyde in Wistar rats. It should be noted that the contribution of formaldehyde, produced metabolically from MTBE, may be different than a drinking water study of formaldehyde in terms of target organ dosimetry. The lack of a lymphoma-leukemia response in F344 rats exposed to MTBE by inhalation may be clouded by the high spontaneous rate of mononuclear cell leukemia in this strain of rat and early mortality in males.

Weight-of-Evidence for Human Hazard

Although there are no published human carcinogenicity studies for MTBE, there are multiple animal studies showing carcinogenic activity and there is supporting animal carcinogenicity data for the MTBE metabolites. With the multiplicity of MTBE tumor responses in two animal species, and by two routes of exposure, one can conclude there is sufficient evidence that MTBE is an animal carcinogen. HEI (1996) concluded "the possibility that ambient levels of MTBE may pose some risk of carcinogenic effects in human populations cannot be excluded". NRC (1996) considered the animal evidence to be positive but "weak" for the purpose of assessing human hazard. Different parties can support more than one conclusion about weight-of-evidence depending on how information about metabolites, pharmacokinetics, mode-of-action hypotheses and the lack of background information for the oral MTBE bioassay is incorporated. We believe the weight-of-evidence supports regarding MTBE as having a carcinogenic hazard potential for humans. The risk assessing community should monitor the ongoing research to see what evolves regarding new studies and modes-of-action research and what these indicate about the likelihood of a human hazard.

Cancer Potency

Once a hazard potential has been established the follow-on task is frequently to characterize the possible impact of exposure on humans. For animal evidence this is done through a dose-response-extrapolation analysis to produce an estimate of possible human risk (i.e., potency) using assumptions and procedures which are not likely to understate the risk. The presentation of estimated cancer potency values in this section provides a crude estimate of possible risk. The act of performing the calculations does not add more certainty to the original hazard weight-of-evidence position or debate. Risk managers must be very cautious about using the estimates for regulatory decision-making purposes and